Endometriosis

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Introduction

Ten percent of women of fertile age are affected by endometriosis, and 30–50% of these women suffer from infertility [1, 2] Due to the chronic progression of the disease, there is a risk of a reduction in the ovarian reserve in these women, both because of the pathophysiology of the disease and because of the possible iatrogenic injury to the ovaries by surgical intervention. Approximately 40–50% of young women experience a recurrence of endometriosis before trying to become pregnant [3, 4].

Fertility preservation in endometriosis follows different principles than in malignant diseases, where there is only a short window of time available before gonadotoxic treatment is started.

Fertility preservation includes carefully determining the indications for a restorative and at the same time fertility-preserving surgical intervention. The aim should also be to try for a pregnancy as early as possible. Fertility preservation measures in the sense of ovarian stimulation and cryopreservation of oocytes (see chapters "Ovarian Stimulation to Collect Oocytes" and "Cryopreservation of Unfertilized and Fertilized Oocytes") are only relevant in young women who are at risk of a relevant reduction in fertility because of disease progression and who do not yet have a current desire to have children or are not yet able to realise it.

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Classification of Endometriosis

rASRM Classification

Endometriosis is divided into several stages, depending on its spread. One of the best-known classifications is the rASRM classification of the American Society for Reproductive Medicine (ASRM) (Fig. 1). Four stages are determined using a scoring system. The resulting rASRM score shows only a weak correlation with symptoms such as dysmenorrhoea and dyspareunia and with the degree and risk of infertility [5, 6].

According to the rASRM classification, endometriosis is divided into the following four stages:

- Stage I (minimal): 1–5 points
- Stage II (mild): 6–15 points
- Stage III (moderate): 16–40 points
- Stage IV (severe): >40 points

ENZIAN Classification

The ENZIAN classification was developed, because the rASRM classification lacks the description of retroperitoneal structures in deeply infiltrating endometriosis. Deep-infiltrating endometriosis is often associated with infertility due to the restricted mobility of the pelvic organs.

The ENZIAN classification should be seen as a complementary classification [8]. Analogous to an oncological TNM (tumour, node = lymph nodes, metastases) classification, it describes the endometriosis lesions in three different anatomical compartments and spatial axes and assigns a severity level to each of them.

- Compartment A comprises the rectovaginal space, extending from the rectouterine pouch towards the vagina.
- Compartment B describes the space lateral to the uterosacral ligaments, extending towards the pelvic wall.
- Compartment C describes the area from the rectovaginal space towards the rectum and includes the rectum.

Pathophysiology of Infertility in Endometriosis

In moderate to severe stages of endometriosis anatomy is altered. The tubal uptake of the oocyte can be severly disturbed due to limited mobility or the closure of the tube(s).

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date_____

Stage I (Minimal): 1-5
Stage II (Mild): 6-15
Stage III (Moderate): 16-40
Stage IV (Severe): >40
Total: _____

Laparoscopy_____ Laparotomy_____ Photography__
Laparoscopic Treatment_____
_____
Prognosis_____

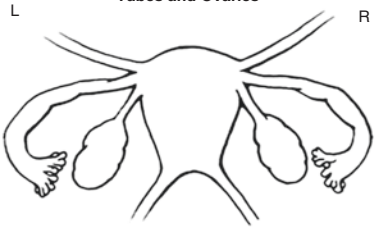
PERITONEUM	ENDOMETRIOSIS	< 1cm	1-3 cm	>3 cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial	Complete	
		4	40	
OVARY	ADHESIONS	< 1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBES	R Filmy	1	2	4
	Dense	4•	8*	16
	L Filmy	1	2	4
	Dense	4•	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis:_____
_____
_____
_____

Associated Pathology:_____
_____
_____
_____

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and Ovaries

Fig. 1 rASRM classifications of endometriosis, describing the spread of endometriosis [7]

The endometriosis foci lead to an inflammatory reaction, which causes various fertility-relevant systems to dysfunction. Higher concentrations of inflammatory cytokines can be detected in the peritoneal fluid [9] as well as in the follicular fluid [10].

The peritoneal fluid which has been altered by inflammation probably influences sperm [11] and tube motility [12].

The endometrium is negatively influenced by free radicals in the peritoneal fluid [13–15]. In women with endometriosis, it contains increased concentrations of pro-inflammatory cytokines [16] and exhibits dysregulation of the progesterone receptor, which can lead to progesterone resistance [17] and thus to a reduced effect of progesterone on the endometrium. This may result in luteal phase dysfunction [18–20].

Ovarian function is influenced by the mechanical stretching of the ovarian cortex in the peripheral area of the endometrioma. Cystic fluid from the endometrioma can lead to an increased concentration of iron in the follicles [21, 22].

As a whole, these factors have a negative effect on conception and embryonic development [12], which is also reflected in a higher miscarriage rate in women with endometriosis [23].

Fertility Preservation Measures

Spontaneous Pregnancy

In patients with endometriosis, the primary goal should be pregnancy if possible, either spontaneously or – if necessary – with the help of reproductive medicine. The chances of a spontaneous pregnancy can be estimated using the Endometriosis Fertility Index (EFI) [31] (Fig. 2). This scoring system calculates the chance of pregnancy based on the functionality of the tubes and ovaries, depending on the age of the woman and the duration of infertility (Fig. 3). The effectiveness of this score has been confirmed by other groups [32].

Surgical Techniques

Surgical clearance not only reduces symptoms, such as dysmenorrhoea and dyspareunia, but can also enhance fertility [33].

However, surgery can reduce the ovarian reserve by damaging the ovary itself and the surrounding tissue [28, 34]. A meta-analysis in 2015 showed that after surgery to remove endometrioma on the affected ovary, fewer oocytes were obtained with IVF and more stimulation cycles were discontinued (Table 1) [30].

ENDOMETRIOSIS FERTILITY INDEX (EFI)
SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description		Left	Right
4	= Normal	Fallopian Tube		
3	= Mild Dysfunction			
2	= Moderate Dysfunction	Fimbria		
1	= Severe Dysfunction			
0	= Absent or Nonfunctional	Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

Lowest Score [ ] (Left) + [ ] (Right) = [ ] (LF Score)

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	**Description**	**Points**	**Factor**	**Description**	**Points**
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			**Total Surgical Factors**		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: [ ] (Historical) + [ ] (Surgical) = [ ] **EFI Score**

Fig. 2 Endometriosis Fertility Index (EFI), which describes the chances of spontaneous conception in patients with endometriosis [31]

On the other hand, endometriomas per se cause a reduction in the ovarian reserve (Table 1) [21, 22], and under certain conditions, it is advisable to seek surgical removal. It has been suggested by individual authors and in the ESHRE guideline [33] that a cystectomy should be performed with an endometrioma size of ≥3 cm, also to rule out malignancy. However, in most cases, it is advisable to determine the indication for surgery individually. The expected surgical damage (Table 1) (reduction in the ovarian reserve) plays a role as well, as does the potential benefit (better accessibility of the ovaries and follicles during follicle aspiration). The patient's current pain situation must also be considered when deciding upon the indication for surgery. Dyspareunia per se can greatly reduce the chances of pregnancy.

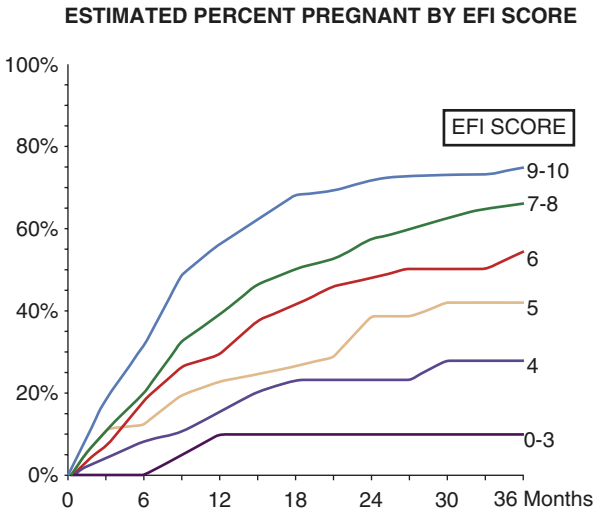


Fig. 3 Endometriosis Fertility Index (EFI), presentation of the estimated conception chances depending on the EFI score [31]

Table 1 Effects of ovarian endometriosis on conception

	Effect on ovarian function	Effect on ovarian reserve	Effect on IVF treatment	Effect on pregnancy rate
Ovarian endometriomas	Mechanical stretching of the ovarian cortex by endometrioma leads to increased ovarian fibrosis and reduced follicle density in 55% of cases [22], and higher iron content in the follicles [21].	Reduction of the ovarian reserve through bilateral endometrioma: Lower serum AMH concentration with bilateral endometrioma: 1.3 ng/mL (Median, interquartile range: 0.5–2.5) versus 2.0 ng/mL (1.1–3.6) with unilateral endometrioma [24].	For bilateral endometrioma, aspiration of fewer oocytes, but the same pregnancy rate as for unilateral endometrioma [25, 26].	Ovulation occurs less frequently in ovaries with endometrioma (31%; 95% CI: 22–43%) [27].
Endometriosis related ovarian surgery		Reduction in serum AMH concentration. Meta-analysis: decrease in AMH concentration by 1.5 ng/mL (95% CI 1.04–2) [28]. Significantly higher decrease after bilateral resection [29].	Higher risk of poor response (<4 oocytes) OR = 2.1; 95% CI: 1.1–4. [25, 26]. Lower number of oocytes retrieved; Mean difference: -2.37 (−3.55 to −1.70) [30].	Reduced pregnancy rate with IVF treatment versus healthy controls (OR 0.53 (95% CI: 0.33–0.84) [30].

The surgical technique has an influence on tissue damage. To reduce the risk of recurrence and alleviate pain symptoms, the cyst should be carefully enucleated. If this is not possible, laser vaporisation is an alternative, especially in cases of bilateral involvement or ovaries which have previously been operated on. Bipolar coagulation and ovariectomy should be avoided [35, 36]. The operation should always be minimally invasive to prevent adhesions. This requires particular surgical expertise.

Cryopreservation of Oocytes

The indication for fertility preservation is given if the bilateral damage to the ovaries is foreseeable, if the woman wants or has to postpone her desire for children and still has a sufficient ovarian reserve.

As a rule, only ovarian stimulation and cryopreservation of mature oocytes are pertinent as a fertility preservation measure. The cryopreservation of ovarian tissue is usually not relevant in endometriosis patients, since tissue removal would further reduce the ovarian reserve and the spontaneous chance of pregnancy after transplantation of ovarian tissue is likely to be low due to intra-abdominal adhesions.

Data on the cryopreservation of oocytes as a fertility-protective measure in women with endometriosis are limited. A case study [37] was published on the cryopreservation of 21 oocytes which have not yet been thawed. A recently published case series showed data from 49 endometriosis patients and a total of 70 cryopreservation cycles. The cohort [38] was divided into three subgroups according to their endometriosis phenotype: peritoneal, ovarian and deep infiltrating. The mean number of cryopreserved oocytes per cycle was 7.2 ± 4.9 in all women. After surgical treatment of ovarian lesions, significantly fewer cells (on average 5.3 ± 3.7 oocytes) could be cryopreserved.

Based on the data from egg donation therapies, problem-free cryopreservation and storage of the oocytes over several years can be assumed. The chances of success depend greatly on the number of oocytes collected and the age of the woman at removal, as well as on the expertise of the centre with cryopreservation [39]. Data on the success rate depending on the age and the number of cryopreserved oocytes for women without endometriosis can be found in chapter “Cryopreservation of Unfertilized and Fertilized Oocytes”. It should be noted, however, that the chances of success are likely to be lower in case of endometriosis due to the factors mentioned above.

Ovarian stimulation to create a fertility reserve only makes sense if the associated chance of a later pregnancy is sufficiently high. The women should therefore be relatively young and still have a sufficient ovarian reserve. The age limit of 35 years and an AMH $\geq$ 1 ng/mL mentioned in Fig. 4 are not based on scientific studies but follows clinical experience.

When determining the indication for cryopreservation of oocytes, the risks of this measure must be considered. Seyhan et al. [40] showed that the volume of endometriomas increased significantly from approx. 22–25 mL and thus by approx. 10% in approx. 80% of cases during a stimulation cycle. The increase in size was

more pronounced in large endometriomas. Assuming that this increase in size is due to high estrogen concentrations, letrozole could be used in addition to gonadotrophins (see chapter "Ovarian Stimulation to Collect Oocytes"). Kim et al. [41] showed that the estrogen concentration was about two-third lower with additional treatment with letrozole, but the oocyte count did not differ. However, it is unclear whether letrozole can also prevent the growth of endometriomas under stimulation.

It should also be noted that follicle aspiration is associated with an increased risk of bleeding and infection due to the often-altered anatomical conditions and endometriomas [42–44]. Endometriomas should not be punctured and antibiotic therapy (e.g. cefuroxime 1.5 mg 3x/day i.v. or 500mg 2x/day orally for up to 4 days) should be considered in the event of an accidental aspiration [44].

Practical Approach

The first step is to decide on the priorities of the procedure. Should the primary goal be spontaneous conception or a surgical intervention? Is the aim a fertility preservation measure with cryopreservation of oocytes? It is also possible that a surgical intervention is planned primarily, but cryopreservation of oocytes is carried out beforehand, as the risk of surgically induced reduction of the ovarian reserve is high.

Ovarian stimulation is performed in the same way as in classical IVF. Drug treatment for endometriosis (e.g. with 2 mg dienogest per day) can probably be continued until 2–3 days before the start of stimulation, as dienogest has a half-life of only 9 h [45]. Continuation of progestin administration during stimulation is not recommended, since otherwise, as with luteal phase stimulation (see chapter "Ovarian Stimulation to Collect Oocytes"), fewer oocytes could be obtained.

The data regarding the benefit of a long or ultra-long agonist protocol with several weeks of prior downregulation is not clear [46]. Although some studies have described a higher birth rate with longer downregulation, this does not mean that this is also beneficial for the cryopreservation of oocytes. It is suspected that long downregulation leads to a beneficial reduction in the endometriosis-related inflammatory reaction, but also to atrophy of adenomyosis, which is often associated with higher grade endometriosis [47]. Both are beneficial for implantation and early embryonic development. However, this positive effect is not relevant in the cryopreservation of oocytes, as no transfer takes place.

For ovarian stimulation the antagonist protocol in combination with ovulation induction with GnRH agonists should be used (see chapter "Ovarian Stimulation to Collect Oocytes"). This protocol reduces the risk of ovarian hyperstimulation syndrome. Premature luteolysis with the associated drop in estrogen concentration should also be beneficial. Surgical treatment of endometriosis should be performed 2 weeks after follicular aspiration at the earliest, i.e. after the end of the luteal phase, as this is when the estrogen and progesterone concentrations have fallen and the corpora lutea have degenerated, which should lead to a lower risk of bleeding.

It is unclear how many stimulation cycles should be carried out and whether they should follow one another directly or if there should be an endocrine therapy phase in between. These questions must be clarified individually, depending on the number of oocytes obtained, the pain caused by endometriosis and the patient's wishes. If the oocytes are later thawed, fertilised and an embryo transfer is carried out, luteal phase support is mandatory, as luteal phase dysfunction is suspected in severe endometriosis [18–20] (Figs. 4 and 5).

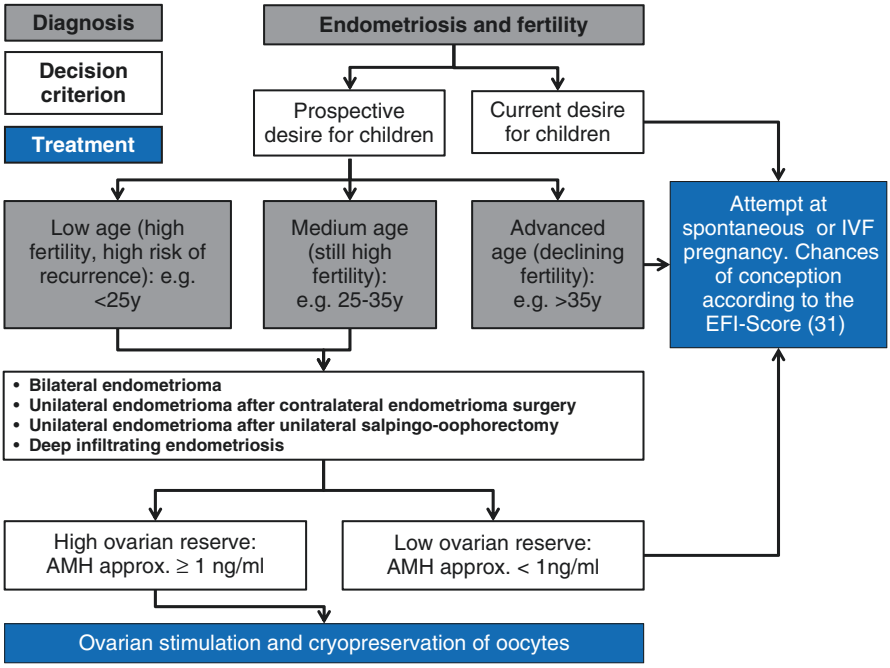


Fig. 4 Algorithm for fertility preservation in patients with endometriosis

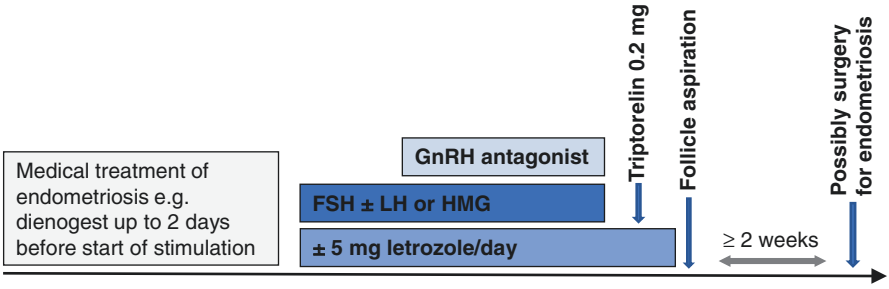


Fig. 5 Stimulation protocol for the cryopreservation of oocytes in patients with endometriosis

References

1. Viganò P, Parazzini F, Somigliana E, Vercellini P. Endometriosis: epidemiology and aetiological factors. Best Pract Res Clin Obstet Gynaecol. 2004;18:177–200.
2. de Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. Lancet. 2010;376:730–8.
3. Brosens I, Gordts S, Benagiano G. Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion. Hum Reprod. 2013;28:2026–31.
4. Benagiano G, Guo S-W, Puttemans P, Gordts S, Brosens I. Progress in the diagnosis and management of adolescent endometriosis: an opinion. Reprod Biomed Online. 2018;36:102–14.
5. Vercellini P, Trespidi L, De Giorgi O, Cortesi I, Parazzini F, Crosignani PG. Endometriosis and pelvic pain: relation to disease stage and localization. Fertil Steril. 1996;65:299–304.
6. Guzick DS, Silliman NP, Adamson GD, Buttram VC, Canis M, Malinak LR, Schenken R. Prediction of pregnancy in infertile women based on the American Society for Reproductive Medicine's revised classification of endometriosis. Fertil Steril. 1997;67:822–9.
7. American Society for Reproductive. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril. 1997;67:817–21.
8. Haas D, Chvatal R, Habelsberger A, Wurm P, Schimetta W, Oppelt P. Comparison of revised American Fertility Society and ENZIAN staging: a critical evaluation of classifications of endometriosis on the basis of our patient population. Fertil Steril. 2011;95:1574–8.
9. Lebovic DI, Mueller MD, Taylor RN. Immunobiology of endometriosis. Fertil Steril. 2001;75:1–10.
10. Wu G, Bersinger NA, Mueller MD, von Wolff M. Intrafollicular inflammatory cytokines but not steroid hormone concentrations are increased in naturally matured follicles of women with proven endometriosis. J Assist Reprod Genet. 2017;34:357–64.
11. Oral E, Seli E, Bahtiyar MO, Olive DL, Arici A. Growth-regulated alpha expression in the peritoneal environment with endometriosis. Obstet Gynecol. 1996;88:1050–6.
12. Lyons RA, Djahanbakhch O, Saridogan E, Naftalin AA, Mahmood T, Weekes A, Chenoy R. Peritoneal fluid, endometriosis, and ciliary beat frequency in the human fallopian tube. Lancet. 2002;360:1221–2.
13. Ota H, Igarashi S, Sato N, Tanaka H, Tanaka T. Involvement of catalase in the endometrium of patients with endometriosis and adenomyosis. Fertil Steril. 2002;78:804–9.
14. Grandi G, Mueller MD, Bersinger NA, Facchinetti F, McKinnon BD. The association between progestins, nuclear receptors expression and inflammation in endometrial stromal cells from women with endometriosis. Gynecol Endocrinol. 2017;33:712–5.
15. McKinnon BD, Kocbek V, Nirgianakis K, Bersinger NA, Mueller MD. Kinase signalling pathways in endometriosis: potential targets for non-hormonal therapeutics. Hum Reprod Update. 2016;22:382–403.
16. Patel BG, Rudnicki M, Yu J, Shu Y, Taylor RN. Progesterone resistance in endometriosis: origins, consequences and interventions. Acta Obstet Gynecol Scand. 2017;96:623–32.
17. McKinnon B, Mueller M, Montgomery G. Progesterone resistance in endometriosis: an acquired property? Trends Endocrinol Metab. 2018;29:535–48.
18. Giudice LC. Endometriosis. N Engl J Med. 2010;362:2389–98.
19. Santamaria X, Massasa EE, Taylor HS. Migration of cells from experimental endometriosis to the uterine endometrium. Endocrinology. 2012;153:5566–74.
20. Vallvé-Juanico J, Houshdaran S, Giudice LC. The endometrial immune environment of women with endometriosis. Hum Reprod Update. 2019;25:565–92.
21. Sanchez AM, Papaleo E, Corti L, Santambrogio P, Levi S, Vigano P, Candiani M, Panina-Bordignon P. Iron availability is increased in individual human ovarian follicles in close proximity to an endometrioma compared with distal ones. Hum Reprod. 2014;29:577–83.
22. Kitajima M, Defrère S, Dolmans M-M, Colette S, Squifflet J, Van Langendonckt A, Donnez J. Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis. Fertil Steril. 2011;96:685–91.

23. Kohl Schwartz AS, Wölfler MM, Mitter V, Rauchfuss M, Haeberlin F, Eberhard M, von Orelli S, Imthurn B, Imesch P, Fink D, Leeners B. Endometriosis, especially mild disease: a risk factor for miscarriages. Fertil Steril. 2017;108:806–14.
24. Somigliana E, Marchese MA, Frattaruolo MP, Berlanda N, Fedele L, Vercellini P. Serum anti-mullerian hormone in reproductive aged women with benign ovarian cysts. Eur J Obstet Gynecol Reprod Biol. 2014;180:142–7.
25. Bourdon M, Raad J, Dahan Y, Marcellin L, Maignien C, Even M, Pocate-Cheriet K, Lamau M, Santulli P, Chapron C. Endometriosis and ART: A prior history of surgery for OMA is associated with a poor ovarian response to hyperstimulation. PLoS One. 2018;13:e0202399.
26. Benaglia L, Bermejo A, Somigliana E, Faulisi S, Ragni G, Fedele L, Garcia-Velasco J. In vitro fertilization outcome in women with unoperated bioateral endometriomas. Fertil Steril. 2013;99:1714–9.
27. Benaglia L, Somigliana E, Vercellini P, Abbiati A, Ragni G, Fedele L. Endometriotic ovarian cysts negatively affect the rate of spontaneous ovulation. Hum Reprod. 2009;24:2183–6.
28. Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2012;97:3146–54.
29. Hirokawa W, Iwase A, Goto M, Takikawa S, Nagatomo Y, Nakahara T, Bayasula B, Nakamura T, Manabe S, Kikkawa F. The post-operative decline in serum anti-Müllerian hormone correlates with the bilaterality and severity of endometriosis. Hum Reprod. 2011;26:904–10.
30. Hamdan M, Dunselman G, Li TC, Cheong Y. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. Hum Reprod Update. 2015;21:809–25.
31. Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. Fertil Steril. 2010;94:1609–15.
32. Tomassetti C, Geysenbergh B, Meuleman C, Timmerman D, Fieuws S, D'Hooghe T. External validation of the endometriosis fertility index (EFI) staging system for predicting non-ART pregnancy after endometriosis surgery. Hum Reprod. 2013;28:1280–8.
33. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W, European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014;29:400–12.
34. Muzii L, Di Tucci C, Di Feliciantonio M, Marchetti C, Perniola G, Panici PB. The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis. Hum Reprod. 2014;29:2190–8.
35. Ferrero S, Venturini PL, Gillott DJ, Remorgida V, Leone Roberti Maggiore U. Hemostasis by bipolar coagulation versus suture after surgical stripping of bilateral ovarian endometriomas: a randomized controlled trial. J Minim Invasive Gynecol. 2012;19:722–30.
36. Muzii L, Achilli C, Bergamini V, Candiani M, Garavaglia E, Lazzeri L, Lecce F, Maiorana A, Maneschi F, Marana R, Perandini A, Porpora M, Seracchioli R, Spangolo E, Vignali M, Benedetti PP. Comparison between the stripping technique and the combined excisional/ablative technique for the treatment of bilateral ovarian endometriomas: a multicentre RCT. Hum Reprod. 2016;31:339–44.
37. Elizur SE, Chian R-C, Holzer HEG, Gidoni Y, Tulandi T, Tan SL. Cryopreservation of oocytes in a young woman with severe and symptomatic endometriosis: a new indication for fertility preservation. Fertil Steril. 2009;91:293.e1–3.
38. Raad J, Sonigo C, Tran C, Sifer C, Cedrin Durnerin I, Grynberg M. Oocyte vitrification for preserving fertility in patients with endometriosis: first observational cohort study and many unresolved questions. Eur J Obstet Gynecol Reprod Biol. 2018;220:140–1.
39. Cobo A, García-Velasco JA. Why all women should freeze their eggs. Curr Opin Obstet Gynecol. 2016;28:206–10.
40. Seyhan A, Urman B, Turkgeldi E, Ata B. Do endometriomas grow during ovarian stimulation for assisted reproduction? A three-dimensional volume analysis before and after ovarian stimulation. Reprod Biomed Online. 2018;36:239–44.

41. Kim SJ, Choo CW, Kim SK, Lee JR, Jee BC, Suh CS, Lee W, Kim S. The effects of letrozole on women with endometriosis undergoing ovarian stimulation for *in vitro* fertilization. Gynecol Endocrinol. 2019;36:257–60.
42. Chen M-J, Yang J-H, Yang Y-S, Ho H-N. Increased occurrence of tubo-ovarian abscesses in women with stage III and IV endometriosis. Fertil Steril. 2004;82:498–9.
43. Yaron Y, Peyser MR, Samuel D, Amit A, Lessing JB. Infected endometriotic cysts secondary to oocyte aspiration for in-vitro fertilization. Hum Reprod. 1994;9:1759–60.
44. Benaglia L, Somigliana E, Iemmello R, Colpi E, Nicolosi AE, Ragni G. Endometrioma and oocyte retrieval–induced pelvic abscess: a clinical concern or an exceptional complication? Fertil Steril. 2008;89:1263–6.
45. von Wolff M, Stute P. Hormonelle Substanzklassen. Gynäkologische Endokrinologie und Reproduktionsmedizin. Schattauer 1. Ausgabe, 2013:5-18.
46. Xue Cao, Hong-yang Chang, Jun-yan Xu, Yi Zheng, Yun-gai Xiang, Bing Xiao, Xu-jing Geng, Li-li Ni, Xi-ying Chu, Shi-bo Tao, Yan He, Gen-hong Mao. The effectiveness of different down-regulating protocols on in vitro fertilization-embryo transfer in endometriosis: a meta-analysis. Reprod Biol and Endocrinol. 2020;18:1.
47. Niu Z, Chen Q, Sun Y, Feng Y. Long-term pituitary downregulation before frozen embryo transfer could improve pregnancy outcomes in women with adenomyosis. Gynecol Endocrinol. 2013;29:1026–30.